

WHAT IS CLAIMED IS:

1. Method for the production of recombinant DNA-derived tissue plasminogen activator (tPA), a tPA variant, a Kringle 2 Serine protease molecule (K2S) or a K2S variant in prokaryotic cells, wherein said tPA, tPA variant, K2S molecule or K2S variant is secreted extracellularly as an active and correctly folded protein, characterized in that the prokaryotic cell contains and expresses a vector comprising the DNA coding for said tPA, tPA variant, K2S molecule or K2S variant operably linked to the DNA coding for the signal peptide OmpA or a functional derivative thereof.

2. Method according to claim 1, characterised in that said the prokaryotic cell contains and expresses a vector comprising the DNA coding for said tPA, tPA variant, K2S molecule or K2S variant operably linked to the DNA coding for the signal peptide OmpA which is operably linked to the nucleic acid molecule defined by the sequence TCTGAGGAAACAGTGAC (SEQ ID NO:1) or a functional derivative thereof.

3. Method according to claim 1 or 2, characterised in that the prokaryotic cell is *E. coli*.

4. Method according to one of claims 1 to 3, characterised in that the the following steps are carried out:

a) the DNA encoding the tPA, tPA variant, K2S molecule or K2S variant is amplified by PCR;

b) the PCR product is purified;

c) said PCR product is inserted into a vector comprising the DNA coding for OmpA signal peptide and the DNA coding for gpIII in such a way that said PCR product is operably linked upstream to the DNA coding for the OmpA signal sequence and linked downstream to the DNA coding for gpIII of said vector;

d) that a stop codon is inserted between said tPA, tPA variant, K2S molecule or K2S variant and gpIII;

e) said vector is expressed by the prokaryotic cell;

f) the tPA, tPA variant, K2S molecule or K2S variant is purified.

5. Method according to one of claims 1 to 4, characterised in that the vector is a phagemid vector comprising the DNA coding for OmpA signal peptide and the DNA coding for gpIII.

6. Method according to one of claims 1 to 5, characterised in that the vector is the pComb3HSS phagemid.

7. Method according to one of claims 1 to 6, characterised in that the DNA Sequence of OmpA linked upstream to K2S comprises the following sequence or a functional variant thereof or a variant due to the degenerate nucleotide code:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG  
CTACCGTGGCCAGGCGGCCTCTGAGGGAAACAGTGACTGCTACTT  
TGGAATGGGTGAGCCTACCGTGGCACGCACAGCCTACCGAGTCG  
GGTGCCTCTGCCTCCCGTGGAATCCATGATCCTGATAGGCAAGG  
TTTACACAGCACAGAACCCAGTGCCAGGCACTGGGCCTGGGCA  
AACATAATTACTGCCGAATCCTGATGGGGATGCCAAGCCCTGGTG  
CCACGTGCTGAAGAACCGCAGGCTGACGTGGGAGTACTGTGATGT  
GCCCTCCTGCTCCACCTGCGGCCTGAGACAGTACAGCCAGCCTCAG  
TTTCGCATCAAAGGAGGGCTCTTCGCCGCATCGCCTCCCACCCCT  
GGCAGGCTGCCATCTTTGCCAAGCACAGGAGGTGCGCCGGAGAGC  
GGTTCCTGTGCGGGGGCATACTCATCAGTCTCCTGCTGGATTCTCTT  
GCCGCCACTGCTTCCAGGAGAGGTTCCGCCCCACCACCTGACGG  
TGATCTTGGGCAGAACATACCGGGTGGTCCCTGGCGAGGAGGAGC  
AGAAATTTGAAGTCGAAAAATACATTGTCCATAAGGAATTCGATGA

TGACACTTACGACAATGACATTGCGCTGCTGCAGCTGAAATCGGAT  
TCGTCCCGCTGTGCCAGGAGAGCAGCGTGGTCCGCACTGTGTGCC  
TTCCCCCGCGGACCTGCAGCTGCCGGA CTGGACGGAGTGTGAGCT  
CTCCGGCTACGGCAAGCATGAGGCCTTGTCTCTCTTCTATTTCGGAG  
CGGCTGAAGGAGGCTCATGTCTAGACTGTACCCATCCAGCCGCTGCA  
CATCACAACATTTACTTTAACAGAACAGTCAACGACAAACATGCTGTG  
TGCTGGAGACACTCGGAGCGGCGGGCCCCAGGCAAACCTTGACACGA  
CGCCTGCCAGGGCGATTCTGGGAGGCCCCCTGGTGTGTCTGAACGAT  
GGCCGCATGACTTTGGTGGGCATCATCAGCTGGGGCTGGGCTGTG  
GACAGAAGGATGTCCCGGGTGTGTACACAAAGGTTACCAACTACCT  
AGACTGGATTCTGTGACAACATGCGACCG (SEQ ID NO:2)

8. Method according to one of claims 1 to 7, characterised in that the DNA Sequence of OmpA comprises the following sequence:  
ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG  
CTACCGTGGCCCAGGCGGCC (SEQ ID NO:3)

9. Method according to one of claims 1 to 8, characterised in that the DNA Sequence of OmpA consists of the following sequence:  
ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG  
CTACCGTGGCCCAGGCGGCC (SEQ ID NO:3)

10. Method according to one of claims 1 to 9, characterised in that the DNA of the tPA, tPA variant, K2S molecule or K2S variant is preceded by a lac promotor and/or a ribosomal binding site.

11. Method according to one of claims 1 to 10, characterised in that the DNA coding for the tPA, tPA variant, K2S molecule or K2S variant is selected from the group of DNA molecules coding for at least 90% of the amino acids 87 – 527, 174 – 527, 180 – 527 or 220 – 527 of the human tissue plasminogen activator protein.

12. Method according to one of claims 5 to 11, characterised in that the DNA Sequence of K2S comprises the following sequence or a functional variant thereof or a variant due to the degenerate nucleotide code:

TCTGAGGGAAACAGTGACTGCTACTTTGGGAATGGGTCAGCCTACC  
GTGGCACGCACAGCCTCACCGAGTCGGGTGCTCTGCCTCCCGTG  
GAATTCCATGATCCTGATAGGCAAGGTTTACACAGCACAGAACCCC  
AGTGCCCAGGCACTGGGCCTGGGCAAAACATAATTACTGCCGGAATC  
CTGATGGGGATGCCAAGCCCTGGTGCCACGTGCTGAAGAACCGCA  
GGCTGACGTGGGAGTACTGTGATGTGCCCTCTGCTCCACCTGCGG  
CCTGAGACAGTACAGCCAGCCTCAGTTTCGCATCAAAGGAGGGCTC  
TTCGCCGACATCGCCTCCCACCCCTGGCAGGCTGCCATCTTTGCCA  
AGCACAGGAGGTGCCCCGGAGAGCGGTTCTGTGCGGGGGCATAAC  
TCATCAGTCTCTGCTGGATTCTCTCTGCCGCCCCTGCTTCCAGGAG  
AGGTTTCCGCCCCACCACCTGACGGTGATCTTGGGCAGAACATACC  
GGGTGGTCCCTGGCGAGGAGGAGCAGAAATTTGAAGTCGAAAAAT  
ACATTGTCCATAAGGAATTCGATGATGACACTTACGACAATGACAT  
TGCGCTGCTGCAGCTGAAATCGGATTCGTCCCCTGTGCCAGGAG  
AGCAGCGTGGTCCGCACTGTGTGCCTTCCCCCGCGGACCTGCAGC  
TGCCGGACTGGACGGAGTGTGAGCTCTCCGGCTACGGCAAGCATG  
AGGCCTTGCTCTCTTTCTATTTCGGAGCGGCTGAAGGAGGCTCATGT  
CAGACTGTACCCATCCAGCCGCTGCACATCACAACATTTACTTAAAC  
AGAACAGTCACCGACAACATGCTGTGTGCTGGAGACACTCGGAGC  
GGCGGGCCCCAGGCAAACCTGCACGACGCCTGCCAGGCGATTCTG  
GGAGCCCCCTGGTGTGTCTGAACGATGGCCGCATGACTTTGGTGG  
GCATCATCAGCTGGGGCCTGGGCTGTGGACAGAAGGATGTCCCGG  
GTGTGTACACAAAGGTTACCAACTACCTAGACTGGATTCTGTGACAA  
CATGCGACCGTGA (SEQ ID NO:4).

13. Method according to one of claims 5 to 12, characterised in that the DNA Sequence of K2S consists of the following sequence:

TCTGAGGGAAACAGTGACTGCTACTTTGGGAATGGGTCAGCCTACC  
GTGGCACGCACAGCCTACCCGAGTCGGGTGCTCTGCTCCCGTG  
GAATTCCATGATCCTGATAGGCAAGGTTTACACAGCACAGAACCC  
AGTGCCCAGGCACTGGGCCTGGGCAAAATAATTACTGCCGAATC  
CTGATGGGGATGCCAAGCCCTGGTGCCACGTGCTGAAGAACCGCA  
GGCTGACGTGGGAGTACTGTGATGTGCCCTCCTGCTCCACCTGCGG  
CCTGAGACAGTACAGCCAGCCTCAGTTTCGCATCAAAGGAGGGCTC  
TTCGCCGACATCGCTCCACCCCTGGCAGGCTGCCATCTTTGCCA  
AGCACAGGAGGTCGCCCCGAGAGCGGTTCTGTGCGGGGGCATAAC  
TCATCAGTCTCTGCTGGATTCTCTCTGCCGCCCCTGCTTCCAGGAG  
AGGTTTCCGCCCCACCACCTGACGGTGATCTTGGGCAGAACATACC  
GGGTGGTCCCTGGCGAGGAGGAGCAGAAATTTGAAGTCGAAAAAT  
ACATTGTCCATAAGGAATTCGATGATGACACTTACGACAATGACAT  
TGCGCTGTGCAGCTGAAATCGGATTCTGCCGCTGTGCCAGGAG  
AGCAGCGTGGTCCGCACTGTGTGCCTTCCCCCGGCGGACCTGCAGC  
TGCCGGACTGGACGGAGGTGTGAGCTCTCCGGCTACGGCAAGCATG  
AGGCCTTGCTCCTTTCTATTTCGGAGCGGCTGAAGGAGGCTCATGT  
CAGACTGTACCCATCCAGCCGCTGCACATCACAACTTTACTTAAC  
AGAACAGTCACCGACAACATGCTGTGTGCTGGAGACACTCGGAGC  
GGCGGGCCCCAGGCAAACCTTGCACGACGCCTGCCAGGGCGATTCTG  
GGAGGCCCCCTGGTGTGTCTGAACGATGGCCGCATGACTTTGGTGG  
GCATCATCAGCTGGGGCCTGGGCTGTGGACAGAAGGATGTCCCGG  
GTGTGTACACAAAGGTTACCAACTACCTAGACTGGATTCTGTGACAA  
CATGCGACCGTGA (SEQ ID NO:4).

14. DNA molecule characterized in that it is coding for:

a) the OmpA protein or a functional derivative thereof operably linked to

b) a DNA molecule coding for a polypeptide containing the kringle 2 domain and the serine protease domain of tissue plasminogen activator protein.

15. DNA molecule according to claim 14, characterized in that said DNA sequence comprises the following sequence or a functional variant thereof or a variant due to the degenerate nucleotide code:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG  
CTACCGTGGCCCAGGCGGCTCTGAGGGAAACAGTGACTGCTACTT  
TGGGAATGGGTCAGCCTACCGTGGCACGCACAGCCTACCGAGTCG  
GGTGCTCTGCTGCCCTCCGTTGGAATTCCATGATCCTGATAGGCAAGG  
TTTACACAGCACAGAACCCAGTGGCCAGGCACTGGGCTGGGCA  
AACATAATTACTGCCGAATCCTGATGGGGATGCCAAGCCCTGGTG  
CCACGTGCTGAAGAACCGCAGGCTGACGTGGGAGTACTGTGATGT  
GCCCTCTGCTCCACCTGCGGCTGAGACAGTACAGCCAGCCTCAG  
TTTCGCATCAAAGGAGGGCTCTTCGCCGACATCGCCTCCCACCCCT  
GGCAGGCTGCCATCTTTGCCAAGCACAGGAGGTGCGCCGGAGAGC  
GGTTCCTGTGCGGGGGCATACTCATCAGCTCCTGCTGGATTCTCTCT  
GCCGCCCCACTGCTTCCAGGAGAGGTTCCGCCCCACCACCTGACGG  
TGATCTTGGGCAGAACATAACCGGTGGTCCCTGGCGAGGAGGAGC  
AGAAATTGAAGTCGAAAAATACATTGTCCATAAGGAATTCGATGA  
TGACACTTACGACAATGACATTGCGCTGCTGCAGCTGAAATCGGAT  
TCGTCCTCGCTGTGCCAGGAGAGCAGCGTGGTCCGCACTGTGTGCC  
TTCCCCCGCGGACCTGCAGCTGCCGGACTGGACGGAAGTGTGAGCT  
CTCCGGCTACGGCAAGCATGAGGCCTGTCTCTTTCTATTCCGAG  
CGGCTGAAGGAGGCTCATGTGAGACTGTACCCATCCAGCCGCTGCA  
CATACAACATTTACTTAACAGAACAGTCAACCGACAACATGCTGTG  
TGCTGGAGACACTCGGAGCGCGGGGCCCCAGGCAAACCTGACGGA  
CGCCTGCCAGGGCGATTCCGGAGGGCCCCCTGGTGTGTCTGAACGAT  
GGCCGCATGACTTTGGTGGGCATCATCAGCTGGGGCTGGGCTGTG  
GACAGAAGGATGTCCCGGTGTGTACACAAAGGTTACCAACTACCT  
AGACTGGATTCTGTGACAACATGCGACCG (SEQ ID NO:5).

16. DNA molecule according to claim 14 or 15, characterized in that said DNA sequence consists of the following sequence:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG  
CTACCGTGGCCCAGGCGGCCTCTGAGGGAAACAGTGA CTGCTACTT  
TGGGAATGGGT CAGCCTACCGTGGCACGCACAGCCTCACCGAGTCG  
GGTGCCTCCTGCCTCCCGTGGAATTCCATGATCCTGATAGGCAAGG  
TTTACACAGCACAGAACCCCA GTGCCAGGCACTGGGCCTGGGCA  
AACATAATTACTGCCGAATCCTGATGGGGATGCCAAGCCCTGGTG  
CCACGTGCTGAAGAACCGCAGGCTGACGTGGGAGTACTGTGATGT  
GCCCTCCTGCTCCACCTGCGGCCTGAGACAGTACAGCCAGCCTCAG  
TTTCGCATCAAAGGAGGGCTCTTCGCGACATCGCCTCCCACCCCT  
GGCAGGCTGCCATCTTTGCCAAGCACAGGAGGTGCGCCGGAGAGC  
GGTTCCTGTGCGGGGGCATACTCATCAGCTCCTGCTGGATTCTCTCT  
GCCGCCC ACTGCTTCCAGGAGAGGTTCCGCCCCACCACCTGACGG  
TGATCTTGGGCAGAACATAACCGGGTGGTCCCTGGCGAGGAGGAGC  
AGAAATTTGAAGTCGAAAAATACATTGTCCATAAGGAATTCGATGA  
TGACACTTACGACAATGACATTGCGCTGCTGCAGTGAAATCGGAT  
TCGTCCCGCTGTGCCCAGGAGAGCAGCGTGGTCCGC ACTGTGTGCC  
TTCCCCCGCGGACCTGCAGCTGCCG GACTGGACGAGTGTGAGCT  
CTCCGGCTACGGCAAGCATGAGGCCTTGCTCTCTTTCTATTCCGAG  
CGGCTGAAGGAGGCTCATGTCAGACTGTACCCATCCAGCCGTGCA  
CATCACAACATTTACTTAACAGAACAGTCAACGACAACATGCTGTG  
TGCTGGAGACACTCGGAGCGCGGGCCCCAGGCAA ACTTGCACGA  
CGCCTGCCAGGGCGATTCTGGGAGGCCCCCTGGTGTGTCTGAACGAT  
GGCCGCATGACTTTGGTGGGCATCATCAGCTGGGCGCTGGGCTGTG  
GACAGAAGGATGTCCCGGTGTGTACACAAAGGTTACCAACTACCT  
AGACTGGATTCTGTACAACATGCGACCG (SEQ ID NO:5).

17. DNA molecule according to one of claims 14 to 16, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 87 – 527 of the human tissue plasminogen activator protein.

18. DNA molecule according to one of claims 14 to 17, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 174 – 527 of the human tissue plasminogen activator protein.

19. DNA molecule according to any one of claims 14 to 18, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 180 – 527 of the human tissue plasminogen activator protein.

20. DNA molecule according to any one of claims 14 to 19, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 220 – 527 of the human tissue plasminogen activator protein.

21. DNA molecule according to any one of claims 14 to 20, characterized in that said DNA sequence a) is hybridizing under stringent conditions to the following sequence:  
ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG  
CTACCGTGGCCAGGCGGCC (SEQ ID NO:6).

22. DNA molecule according to any one of claims 14 to 21, characterized in that said DNA sequence a) consists of the following sequence:  
ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG  
CTACCGTGGCCAGGCGGCC (SEQ ID NO:6).

23. DNA molecule according to any one of claims 14 to 22, characterized in that said DNA sequence b) is hybridizing under stringent conditions to the following sequence:  
TCTGAGGGAAACAGTGA CTGCTACTTTGGAATGGGTCAGCCTACC  
GTGGCACGCACAGCCTCACCAGTCGGGTGCTCCTGCCTCCCGTG  
GAATTCCATGATCCTGATAGGCAAGGTTTACACAGCACAGAACCC



AGTGCCCAAGGCACTGGGCCTGGGCAAAACATAATTACTGCCGGAATC  
CTGATGGGGATGCCAAGCCCTGGTGCCACGTGCTGAAGAACC  
GGCTGACGTGGGAGTACTGTGATGTGCCCTCCTGCTCCACCTGCGG  
CCTGAGACAGTACAGCCAGCCTCAGTTTCGCATCAAAGGAGGGGCTC  
TTCGCCGACATCGCCTCCACCCCTGGCAGGCTGCCATCTTTGCCA  
AGCACAGGAGGTGCGCCGGAGAGCGGTTTCTGTGCGGGGGCATA  
TCATCAGCTCCTGCTGGATTCTCTGTGCCGCCCCTGCTTCCAGGAG  
AGGTTTCCGCCCCACCACCTGACGGTGATCTTGGGCAGAACATAACC  
GGGTGGTCCCTGGCGAGGAGGAGCAGAAATTTGAAGTCGAAAAAT  
ACATTGTCCATAAGGAATTCGATGATGACACTACGACAATGACAT  
TGCGTGCTGTCAGCTGAAATCGGATTCGTCCCCTGTGCCCAGGAG  
AGCAGCGTGGTCCGCACTGTGTGCCTTCCCCCGGCGGACCTGCAGC  
TGCCGGACTGGACGGAGTGTGAGCTCTCCGGCTACGGCAAGCATG  
AGGCCTTGTCTCCTTTCTATTTCGGAGCGGCTGAAGGAGGCTCATGT  
CAGACTGTACCCATCCAGCCGCTGCACATCACAACATTTACTTAAC  
AGAACAGTCACCGACAACATGCTGTGTGCTGGAGACACTCGGAGC  
GGCGGGCCCCAGGCAAACCTTGACACGACGCCTGCCAGGGCGATTCTG  
GGAGGCCCCCTGGTGTGTCTGAACGATGGCCGCATGACTTTGGTGG  
GCATCATCAGCTGGGGCCTGGGCTGTGGACAGAAGGATGTCCCGG  
GTGTGTACACAAAGTTACCAACTACCTAGACTGGATTCTGTGACAA  
CATGCGACCGTGA (SEQ ID NO:7).

24. DNA molecule according to any one of claims 14 to 23, characterized in that said DNA sequence b) consists of the following sequence:

TC TGAGGGAAACAGTGACTGCTACTTTGGGAATGGGT CAGCCTACC  
GTGGCACGCACAGCTCACCAGT CGGGTGCTCTGCTCCCGTG  
GAATTCATGATCCTGATAGGCAAGGTTTACACAGCACAGAACCC  
AGTGCCCAAGGCACTGGGCCTGGGCAAAACATAATTACTGCCGGAATC  
CTGATGGGGATGCCAAGCCCTGGTGCCACGTGCTGAAGAACC  
GGCTGACGTGGGAGTACTGTGATGTGCCCTCCTGCTCCACCTGCGG

CCTGAGACAGTACAGCCAGCCTCAGTTTCGCATCAAAGGAGGGCTC  
TTCGCCGACATCGCCTCCCACCCCTGGCAGGCTGCCATCTTTGCCA  
AGCACAGGAGGTCGCCCGGAGAGCGGTTCTGTGCGGGGCATAC  
TCATCAGCTCCTGCTGGATTCTCTGCGCGCCACTGCTTCCAGGAG  
AGGTTTCCGCCCCACCACTGACGGTGATCTTGGGCAGAACATACC  
GGGTGGTCCCTGGCGAGGAGGAGCAGAAATTTGAAGTCGAAAAAT  
ACATTGTCCATAAGGAATTCGATGATGACACTTACGACAATGACAT  
TGCGCTGCTGCAGCTGAAATCGGATTCGTCCCGCTGTGCCCAGGAG  
AGCAGCGTGGTCCGCACTGTGTGCCTTCCCCGGCGGACCTGCAGC  
TGCCGGACTGGACGGAGTGTGAGCTCTCCGGCTACGGCAAGCATG  
AGGCCTTGTCTCCTTTCTATTTCGGAGCGGCTGAAGGAGGCTCATGT  
CAGACTGTACCCATCCAGCCGCTGCACATCACAACATTTACTTAAC  
AGAACAGTCACCGACAACATGCTGTGTGCTGGAGACACTCGGAGC  
GGCGGGCCCCCAGGCAAACCTTGACACGACGCCTGCCAGGGCGATTCTG  
GGAGGCCCCCTGGTGTGTCTGAACGATGGCCGCATGACTTTGGTGG  
GCATCATCAGCTGGGGCCTGGGCTGTGGACAGAAGGATGTCCCGG  
GTGTGTACACAAAGGTTACCAACTACCTAGACTGGATTCTGTGACAA  
CATGCGACCGTGA (SEQ ID NO:7).

25. Fusion protein of OmpA and K2S, characterised in that it comprises a protein characterized by the following amino acid sequence or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative or a glycosylation variant thereof:

MKKTAIAlAVALAGFATVAQAASEGNSDCYFNGSAYRGTHSLTESG  
ASCLPWNMILIGKVYTAQNPSAQLGLGKHNYCRNPDGDAKPWCH  
VLKNRRLTWEYCDVPSCSTCGLRQYSQPQFRIKGGLFADIASHPWQA  
AIFAKHRRSPGERFLCGGILISSCWILSAAHCFQERFPPHHLTIVILGR  
TYRVVPGEEEKFEVEKYIVHKEFDDDTYDNDIALQLKSDSSRCAQESS  
VVRTVCLPPADLQLPDWTECELSGYGKHEALSPFYSERLKEAHVRLYP  
SSRCTSQHLLNRTVTDNMLCAGDTRSGGPQANLHDACQGDSSGGLVC

LNDGRMTLVGIISWGLGCGQKDVPGVYTKVTNYLDWIRDNM RPG  
(SEQ ID NO:8).

26. Fusion protein of OmpA and K2S according to claim 25, characterised in that it consists of a protein characterized by the following amino acid sequence:

MKKTAIAIAVALAGFATVAQAASEGNSDCYFGNGSAYRGTHSLTESG  
ASCLPWNSMILIGKVYTAQNPSAQALGLGKHNCRNPDGDAKPWCH  
VLKNRRLTWEYCDVPSCSTCGLRQYSQPQFRIKGGLFADIASHPWQA  
AIFAKHRRSPGERFLCGGILISSCWILSAAHCFQERFPPHHLTIVLGRTY  
RVVPGEEEQKFEVEKYIVHKEFDDDTYDNDIALQLKSDSSRCAQESS  
VVRTVCLPPADLQLPDWTECELSGYGKHEALSPFYSERLKEAHVRLYP  
SSRCTSQHLLNRTVTDNMLCAGDTRSGGPQANLHDACQGDSSGGLVC  
LNDGRMTLVGIISWGLGCGQKDVPGVYTKVTNYLDWIRDNM RPG  
(SEQ ID NO:8).

27. K2S protein, characterised in that it comprises a protein defined by the sequence SEGN (SEQ ID NO:9) and a or a variant or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative, a fusion protein or a glycosylation variant thereof.

28. K2S protein according to claim 27, characterised in that it comprises a protein defined by the sequence SEGNSD (SEQ ID NO:10) and a or a variant or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative, a fusion protein or a glycosylation variant thereof.

29. K2S protein according to claim 28 or 29, characterised in that it comprises a protein characterized by the following amino acid sequence or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative or a glycosylation variant thereof:

SEGNSDCYFGNGSAYRGTHSLTESGASCLPWNSMILIGKVYTAQNPSA  
QALGLGKHNCRNPDGDAKPWCHVLKNRRLTWEYCDVPSCSTCGLR  
QYSQPQFRIKGGLFADIASHPWQAAIFAKHRRSPGERFLCGGILISSCWI  
LSAAHCFQERFPPHLLTVILGRTYRVVPGEEEQKFEVEKYIVHKEFDD  
DTYDNDIALQLKSDSSRCAQESSVVRTVCLPPADLQLPDWTECELSG  
YGKHEALSPFYSERLKEAHVRLYPSSRCTSQHLLNRTVTDNMLCAGD  
TRSGGPQANLHDACQGDGGPLVCLNDGRMTLVGIISWGLGCGQKD  
VPGVYTKVTNYLDWIRDNMRP\* (SEQ ID NO:11).

30. K2S according to any one of claims 27 to 30, characterised in that it consists of a protein characterized by the following amino acid sequence:

SEGNSDCYFGNGSAYRGTHSLTESGASCLPWNSMILIGKVYTAQNPSA  
QALGLGKHNCRNPDGDAKPWCHVLKNRRLTWEYCDVPSCSTCGLR  
QYSQPQFRIKGGLFADIASHPWQAAIFAKHRRSPGERFLCGGILISSCWI  
LSAAHCFQERFPPHLLTVILGRTYRVVPGEEEQKFEVEKYIVHKEFDD  
DTYDNDIALQLKSDSSRCAQESSVVRTVCLPPADLQLPDWTECELSG  
YGKHEALSPFYSERLKEAHVRLYPSSRCTSQHLLNRTVTDNMLCAGD  
TRSGGPQANLHDACQGDGGPLVCLNDGRMTLVGIISWGLGCGQKD  
VPGVYTKVTNYLDWIRDNMRP\* (SEQ ID NO:11).

31. A vector containing a DNA sequence according to any one of claims 14 to 24.

32. A vector according to claim 31, wherein said DNA sequence is preceded by a lac promoter and a ribosomal binding site.

33. The vector pComb3HSS containing a DNA according to any one of claims 14 to 24, wherein the expression of the gp III protein is suppressed or inhibited by deleting the DNA molecule encoding said gp III protein or by a stop codon between the gene coding for a polypeptide

containing the kringle 2 domain and the serine protease domain of tissue plasminogen activator protein and the protein III gene.

34. A prokaryotic host cell comprising a DNA molecule according to any one of claims 14 to 24.

35. A prokaryotic host cell comprising a vector according to any one of claims 31 to 33.

36. An *E. coli* host cell comprising a DNA molecule according to any one of claims 14 to 24.

37. An *E. coli* host cell comprising a vector according to any one of claims 31 to 33.

38. Use of a DNA molecule according to any one of claims 14 to 24 or of a vector according to any one of claims 31 to 33 or a host cell according to any one of claims 34 to 37 in a method for the production of a polypeptide having the activity of tissue plasminogen activator.

39. Use according to claim 38, wherein said method is a method according to any one of claims 1 to 13.